REMARKS

Amendments to the Claims

Claims 23 and 30 have been canceled.

Claims 15 and 16 have been amended to delete "selected from the group consisting of... an HMG1L1 A box, an HMG1L4 A box, an HMGB A box polypeptide of BAC clone RP11-395A23, an HMG1L9 A box, an LOC122441 A box, an LOC139603 A box, and an HMG1L8 A box".

Claims 15, 16 and 24 have been amended to delete the term "or variant thereof".

The amended claims are supported by the subject application as originally filed. Therefore, this Amendment adds no new matter.

Additional remarks are set forth below with reference to the numbered paragraphs in the Office Action.

Paragraph 4. Rejection of Claims 15-16 and 20-33 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 15-16 and 20-33 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the Examiner's opinion, the claims only describe the compositions of interest by an arbitrary protein name, "HMG1B1 A box". Specifically, the Examiner states that "[c]laiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and of what compositions comprising that protein are made." (Office Action, page 2). The Examiner suggests pointing out and distinctly claiming the A box by claiming characteristics associated with the protein (e.g. activity, molecular weigh, amino acid composition, N-terminal sequence, etc.) to distinctly identify the protein.

To clarify, the claims recite an HMGB A box, not an HMG1B1 A box as the Examiner indicates. The HMGB A box is not an arbitrary name used only by some scientists in the field, but is a term recognized and understood by those of skill in the art (See, for example, Taudte, S.,

et al., Protein Eng., 14(12): 1015-1023 (2001); Reference C65 of record.) Furthermore, "HMGB A box" is defined in the specification at page 15, line 28 through page 18, line 6. In addition, the applicant has further defined the term "HMGB A box" in the claim by the functional limitation that the protein "can inhibit release of a proinflammatory cytokine from a cell" and that the A box protein must be an HMG1L5 A box.

Reconsideration and withdrawal of the rejection are requested.

Paragraph 6. Rejection of Claims 15-16 and 20-33 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 15-16 and 20-33 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the Examiner's opinion, there is insufficient guidance and direction as to make and use any "condition in a patient characterized by activation of an inflammatory cytokine cascade." (Office Action, page 3). The Examiner further states that the specification fails to provide *in vivo* data to show that the method would work and fails to show any HMGB A box polypeptide, including the one encoded by pseudogenes, would work.

The Examiner asserts that the specification does not provide sufficient enablement to treat, for example, graft-versus-host disease ("GVHD") caused by Th1 cell-mediated immune response or by a Th2 cell mediated immune response. The Examiner further asserts that Dallman (Current Opinion in Immunology, *7*:632-638 (1995)) teaches that both Th1 and Th2 cells are involved in graft rejection response, and that Dallman concluded that it is difficult to make a case that graft rejection is caused by an immune response driven by either Th1 or Th2 cells alone. The Examiner also cites to Krenger and Ferrara (Immunol. Res., *15*:50-73 (1996)) and asserts that they teach that the development of acute GVHD is a three-step process and that distinct immunological patterns are associated with differential activation of Type 1 and Type 2 T cells subsets after allogenic BMT. The Examiner concludes that the specification does not provide sufficient enablement for the treatments of both chronic and severe lethal acute GVHD syndrome. (Office Action, pages 3-4).

Applicants are not required to demonstrate their claimed method would work on each and every disease imaginable, but rather provide enablement for a representative number of species.

Representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation. The Applicant has shown that HMGB1 A Box protein successfully treats mice during sepsis. (Specification, Example 12, page 63). The specification further teaches that sepsis is one of several conditions characterized by activation of an inflammatory cytokine cascade. (Specification, pages 30-32).

Furthermore, it is well-settled law that the enablement and utility requirements of the patent law do not impose on applicants for patents the burden of proving clinical safety and efficacy (see, *e.g.*, M.P.E.P. §§ 2107.01(III-IV), p. 2100-34-37 and 2107.3(V), p. 2100-45-46 (8th Ed., 3rd Rev., August 2005). Therefore, the applicant has no duty to provide *in vivo* data in humans to show that the claimed method would work.

The Examiner further asserts that Friend *et al.* (Transplantation, *68*:1625-1631 (1999); hereinafter "Friend") teach that monoclonal antibodies have proved to be of immense importance from a diagnostic and investigative standpoint, but their impact on therapeutic regimens in clinical transplantation has been rather disappointing. (Office Action, page 4).

In fact, the assertion above was not taught by Friend, but was provided as a commentary by Wood and Pockley on the research reported elsewhere in the journal by Friend. The commentators assert that the clinical application of monoclonal antibodies is restricted by the development of a humoral immune reaction to the mouse or rat immunoglobulin protein, but the research by Friend in this same journal issue reports a Phase I study of an antibody in renal transplant recipients. Indeed, Friend provided evidence of improvements in renal function and biopsy appearances in the majority of the treated patients. Even the commentators agreed that "[t]he generation of engineered antibodies that are capable of treating/reversing graft rejection without concomitant toxicity is exciting." (last paragraph, page 1625). Therefore, in contrast to assertion of disappointment made by the Examiner, this reference demonstrates the positive impact that humanized antibodies can have in the clinic.

The Examiner further asserts that the specification fails to provide guidance on which organ can be transplanted using the claimed methods and does not provide sufficient enablement for transplanting any organ or any tissue rejection. The Examiner asserts that Toogood *et al.* (Transplantation, *62*:851-855 (1996); hereinafter "Toogood") teach that the mechanisms of

rejection in small bowel and other solid organ grafts are likely to be different. The Examiner also asserts that Toogood concluded that there are significant immunological differences between the gut wall compartment of a small bowel transplant and other vascularized allografts. Therefore, the Examiner concludes that it is not clear that the skilled artisan could predict the efficacy of the "HMGB A box" to treat any condition including any organ or tissue rejection.

Applicant respectfully disagrees. It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

Therefore, despite the fact that there may be different mechanisms of rejection between the gut wall compartment of a small bowel transplant and other vascularized allografts, Applicant is claiming a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade. The activation of an inflammatory cytokine cascade is not necessarily different when different mechanisms of rejection are involved in different organ transplantations. Thus, only routine experimentation by one skilled in the art is required to practice the invention as claimed. As the specification teaches, "[t]he route of administration and the dosage of the composition to be administered can be determined by the skilled artisan, without undue experimentation, in conjunction with standard dose-response studies." (Specification, page 32).

The Examiner further asserts that Freeman *et al.* (hereinafter "Freeman") teach that mediator-specific antagonists, high-dose glucocorticoids and endotoxin-directed therapies were administered initially in animal models with promising results, that subsequent administration to humans has proved disappointing, thereby prompting questions regarding the initial hypothesis and value of animal studies in modeling human sepsis (Office Action, page 4). The Examiner asserts that Freeman teaches that many of the issues pertaining to the pathophysiology and treatment of sepsis remain unresolved, and that due to the lack of predictability in the art at the

time the invention was made, an undue amount of experimentation would have been required to practice the claimed invention with a reasonable expectation of success (Office Action, page 4).

While Freeman asserts that clinical trials using proinflammatory mediator-specific antagonists (e.g., interleukin-1 receptor antagonists (IL-1ra), soluble tumor necrosis factor-α (TNF-α) receptors, etc.) in humans with sepsis gave disappointing results (Freeman, page 965, column 1), their meta-analysis of over 20 clinical trials did reveal a small beneficial effect on survival. As summarized by Freeman:

- Mediator-specific non-glucocorticoid anti-inflammatory agents improve outcome, but their beneficial effect is small. Overall, these studies support a role for excessive inflammation in the pathogenesis of sepsis. However, the role for any single circulating mediator appears minimal since circulating mediator-specific inhibition has only modest effects on patients with sepsis.
- Individual sepsis trials to date appear to have overestimated the treatment effect of mediator-specific antiinflammatory therapies, and consequently did not enroll a sufficient number of patients to demonstrate a statistically significant effect on outcome. We estimate that these agents reduce mortality by approximately 7% to 10%, and would require a clinical trial enrolling 6,000 to 7,000 patients to demonstrate a statistically significant beneficial effect on survival rates.

(Freeman, pages 971-72, emphasis added).

Thus, based on their detailed analysis of a large number of studies, Freeman concludes that the use of mediator-specific antagonists "in humans with sepsis actually does produce a small beneficial effect on survival. . . . (i.e., approximately a 7-8% decrease in mortality)" (Freeman, page 974, first paragraph). Moreover, Freeman offers a possible explanation for the observed discrepancy between the beneficial effects in animal studies and human clinical trials, namely that the variables that potentially alter the effects of anti-inflammatory agents (e.g., type and site of bacterial infection, timing of administration of anti-inflammatory therapy, and the use of supportive measures) were not thoroughly evaluated in animal models (Freeman, page 973,

section entitled "Were Animal Models Predictive of the Effects of Anti-Inflammatory Agents in Humans").

Therefore, given the teachings in the specification of methods of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade, and studies demonstrating a therapeutic benefit in human (*e.g.*, as taught by Freeman), the claimed method comprising treating sepsis is clearly enabled.

The Examiner asserts that "it cannot be seen how a polypeptide comprising the HMGB A box, which reads on the full-length, would *inhibit* release of a proinflammatory cytokine from a cell."

Applicant respectfully disagrees. The claim does not read on full length HMGB because the claim recites functional limitations that the polypeptide "can inhibit release of a proinflammatory cytokine from a cell." Thus, the claim does not read on any polypeptide which *stimulates* proinflammatory cytokine release.

The Examiner further asserts that Atwood teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." (Office Action, page 4). The Examiner asserts that the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and that is was difficult to predict if any functional activity would be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Applicant respectfully disagrees with this assertion. Nevertheless, Applicant has deleted "variants" solely to speed prosecution of this application.

The Examiner asserts that the specification discloses the amino acid sequence of a human, mouse and rat HMG1 A box polypeptide as SEQ ID NO:4, but the HMGB1 related sequences are encoded by pseudogenes or very similar genes. The Examiner further asserts that the specification fails to show that the non-functional polypeptides encoded by the pseudogenes represent a functional HMGB A box that would inhibit release of a proinflammatory cytokine from any cell, because while the specification discloses that A box protein inhibits full length HMGB1 and HMGB1 B box cytokine activity (Examples 6 and 7), it fails to disclose which "HMGB A box" was used in the *in vitro* experiments as antagonist of HMGB1 activity in the

macrophage culture experiments to inhibit the TNF-stimulating activity of HMGB1. (Office Action, pages 4-5)

The Examiner asserts that *in vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients and thus, it is not clear that reliance on the HMGB1 A box that inhibits HMGB1 cytokine activity by binding to it accurately reflects the relative efficacy of the claimed "method of treating" in a subject by active immunization with HMGB1 A box polypeptide. (Office Action, page 5).

As explained above, the Applicant has no duty to provide *in vivo* clinical data to show that the claimed method would work, or to prove a certain level of efficacy. It is well within the expectations of one skilled in the art that they would need to perform a certain amount of experimentation to determine the efficacy of the claimed method in a patient. Routine experimentation is expected, as the amount needed will vary based on, for example, the patients and severity of the conditions to be treated.

The Examiner asserts that Claims 25 and 32 recite an antagonist of an early sepsis mediator, however the specification fails to disclose any early sepsis mediators besides the TNF antagonist. (Office Action, page 5). Applicants respectfully disagree with the Examiner. The specification defines an early sepsis mediator as "a proinflammatory cytokine that is released from cells soon (i.e., within 30-60 min.) after induction of an inflammatory cytokine cascade (e.g., exposure to LPS)." (Specification, page 34, lines 9-11). The applicant further provides a list of nonlimiting examples including TNF, IL-1α, IL-1β, IL-6, PAF and MIF. (See, for example, page 34, lines 11-12). Accordingly, the specification does not fail to disclose early sepsis mediators other than TNF.

The Examiner concludes that "[i]n view o[f] the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention." The applicant respectfully disagrees and points to the arguments above for support. In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 8. Claims 15-16, 20-22, 24-29 and 31-33 Under 35 U.S.C. § 102(e)(1)

The Examiner has rejected Claims 15-16, 20-22, 24-29 and 31-33 under 35 U.S.C. § 102(e)(1) as being anticipated by US/2003-0060410 A1 (Tracey *et al.*; hereinafter "the '410 application"). The Examiner asserts that the '410 application teaches the following:

i) a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to the patient a polypeptide comprising a vertebrate high mobility group protein (HMG) A box or a non-naturally occurring HMG A box which can inhibit release of a proinflammatory cytokine from a vertebrate cell treated with high mobility group (HMG) protein in an amount sufficient to inhibit release of the proinflammatory cytokine from the cell;

ii) a composition comprising any of the polypeptides can inhibit a condition characterized by activation of an inflammatory cytokine cascade, where the condition can be one where the inflammatory cytokine cascade causes a systemic reaction, such as with endotoxic shock, rheumatoid arthritis, allograft rejection or sepsis; and

iii) that the composition can further comprise an antagonist of an early sepsis mediator, preferably an antagonist of a cytokine selected from the group consisting of TNF, IL-1α, IL-1β, MIF and IL-6, more preferably, an antibody to TNF or MIF, or an IL-1 receptor antagonist. (Office Action, page 6).

The invention of the subject application, which is based on the discovery that the specific claimed HMGB A box homolog can inhibit release of a proinflammatory cytokine from a cell, and claims a patentably distinct invention, namely a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade with a polypeptide comprising a specific HMGB A box. The specific HMGB A box homolog claimed in the present application is not disclosed in the '410 application. Accordingly, since the '410 application does not teach each and every aspect of Applicant's claimed invention, the claimed methods are not anticipated by the '410 application. Reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 9. Claims 15-16 and 20-33 Under 35 U.S.C. § 102(e)(1)

The Examiner has rejected Claims 15-16 and 20-33 under 35 U.S.C. § 102 (e)(1) as being anticipated by US/2003/0144201 A1. (Tracey *et al.*; hereinafter "the '201 application"). The Examiner asserts that the '201 application teaches the following:

i) a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to the patient a polypeptide comprising a vertebrate high mobility group protein (HMG) A box or a non-naturally occurring HMG A box which can inhibit release of a proinflammatory cytokine from a vertebrate cell treated with high mobility group (HMG) protein in an amount sufficient to inhibit release of the proinflammatory cytokine from the cell, wherein the HMG A box is published SEQ ID NO:25 (claimed HMG1L1 A box);

ii) a composition comprising any of the polypeptides can inhibit a condition characterized by activation of an inflammatory cytokine cascade, where the condition can be one where the inflammatory cytokine cascade causes a systemic reaction, such as with endotoxic shock, rheumatoid arthritis, allograft rejection or sepsis; and

iii) that the composition can further comprise an antagonist of an early sepsis mediator, preferably an antagonist of a cytokine selected from the group consisting of TNF, IL-1α, IL-1β, MIF and IL-6, more preferably, an antibody to TNF or MIF, or an IL-1 receptor antagonist.

(Office Action, page 7).

Claims 15 and 16 have been amended. The invention of the subject application, which is based on the discovery that specific HMGB A box homologs can inhibit release of a proinflammatory cytokine from a cell, claims a patentably distinct invention, namely a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade with a polypeptide comprising a specific HMGB A box. The specific HMGB A box homolog claimed in the present application is not described in the '201 application. Accordingly, since the '201 application does not teach each and every aspect of Applicant's claimed invention, the claimed methods are not anticipated by the '201 application. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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